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ON THE PHYSIOLOGICAL NATURE OF THE "GLANDULAR HYPERPLASIAS" OF DOG'S THYROIDS  
WITH A DETAILED REPORT OF A CASE  
TYPICAL OF THE GROUP.\*

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IN a previous communication<sup>1</sup> it was stated that 90 per cent of all the street dogs in the district of Cleveland showed on histological examination of the thyroids the so called "glandular hyperplasia." It was also stated that the most reasonable deduction from this observation was to consider this hyperplasia as a "Physiologic reaction to a deficiency." It was further stated that on purely anatomic grounds I had reason to believe that glands which once showed this hyperplasia had reverted to a more normal type, suggesting that in these cases the deficiency had been met. No suggestion was then offered as to what this deficiency might be, and it is in this connection that I wish to report a case and bring forward some deductions gathered from a review of the literature on thyroid affections.

This case typifies, I think, the general group of "glandular hyperplasias" in the dog, which I have reason to believe are cretinoid in nature. The dog came under observation October 18, 1906. No previous history was obtainable. The notes of the case as made from time to time are as follows:

The patient is a male, mongrel, bull-terrier puppy, probably five to six weeks old, and weighing roughly 2.728 kilos (5½ lbs.). He is somewhat emaciated and markedly pot-bellied. The bony prominences are distinct. The hair is tawny, dry, coarse, and without gloss. There is a constant overflow of tear-fluid which keeps both cheeks streaked with moisture. The eyes are prominent, but for the species not abnormally so. The thyroid lobes are markedly and apparently symmetrically enlarged. The veins over the goitre are distended, at times more markedly than at others, and definitely pulsate synchronously with the auricular systole. The thyroid lobes, each about the size and of the shape of a hen's egg, are moderately soft and have an expansile pulsation accompanied by a bruit. The tumors vary in size, evidently depending on the amount of blood they contain. They seem larger in the evening than in the morning. The puppy becomes easily fatigued, becomes quite dyspneic, and during these spells the thyroids are notably larger. There is a con-

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stant fine tremor not relieved by heat. The legs are always cold. The mental condition is marked by apathy, sluggishness, and seeming indifference to his surroundings. The appetite is good; stools soft and unformed.

The dog was kept on a milk diet until October 28, but without any evident improvement. I wished to remove a lobe for a control and histological examination, but thinking the risk of operation too great at the time the following was administered:

October 28. 3 gtt. sat. alc. sol. iodine in milk.  
 October 30. 2 " " " " " " " "  
 November 1. 2 " " " " " " " "  
 November 2. 2 five gr. tablets, desiccated thyroid (Armour).  
 November 4. 2 " " " " " ( " ).  
 November 6. 2 " " " " " ( " ).  
 November 6. 2 gtt. sat. alc. sol. iodine in food.

November 7. There is a distinctly noticeable change in the dog's physical and mental condition. He is more active, cheerful, playful, comes at beckoning, and takes notice of his surroundings. The abdomen is less distended. The feces are soft but formed. The thyroid gland is quite firm, though the vessels are large and pulsation is felt. The heart rate has never been accelerated, but systole of the ventricles produces a distinct shock. Tremor still persists.

His condition was considered sufficiently improved to stand an operation and under ether the right lobe was removed. The gross appearance of the gland is as follows: The vessels of the lobe are very large and tortuous; the gland is extremely vascular and the capsule is slightly thickened. The lobes are joined across the midline by a band of thyroid tissue 1 c.m. wide  $\times \frac{1}{2}$  cm. thick. (This condition is quite common in goitrous puppies; Halsted noted this in the litters of goitrous puppies which came to his notice.) On section the lobe is moist, soft, cellular, and grayish pink in color. A slight amount of thin colloid exudes. The acini are not visible. The gland measures  $7 \times 4 \times 3.5$  cm. and weighs 28 grams. Microscopic appearance is given later. The dog stood the anesthetic well and rallied quickly, little ether being necessary. The hemoglobin seemed low. Milk diet.

November 9. Dog is active, cheerful, with appetite good. Heart rate has been rapid since operation.

November 12. 1 five gr. tablet desiccated thyroid, and 2 gtt. sat. alc. sol. iodine. Milk diet to which some bread is added and for the first time a little meat.

November 14. Puppy is mentally alert and playful. The skin is softer, but the hair, however, still dry and coarse. Wound has healed per primam, bandage removed.

November 15. 2 five gr. thyroid tablets.

November 16. 2 " " " "

November 19. The dog is given a bath and large quantities of loose, dead hair are removed, together with considerable desquamated epithelium. After removal of the dead hair a crop of fine, short, glossy hair is visible. One five-grain thyroid tablet given, and 2 gtt. sat. alc. sol. iodine. The remaining lobe is smaller and firmer than immediately after operation. No expansile pulsation. Dog is growing rapidly. Mentally he appears to be a normal dog. Body temperature is higher, extremities are warm. Heart rate is still rapid. Fine tremor has disappeared.

November 22. One five-grain thyroid tablet; the dog, continues to shed dead hair and epidermis and the fine glossy coat is now quite in evidence.

November 28. Hair and skin normal; growing fast; appetite good.

December 11. Growing rapidly; mentally and physically a normal dog save that the heart is still somewhat rapid and the impulse forcible. The gland is firm, pulsation absent, distinctly reduced in size.

This afternoon a "V"-shaped piece of the remaining lobe was removed for microscopic examination. The tissue is quite vascular, pink, translucent gray in color, and firm to the touch. The acini are visible and their colloid content appears normal.

December 17. Dog seems perfectly normal. Wound has healed. Diet of bread milk and a little meat.

January 14, 1907. Killed. Weight 6.2 kilos (12.5 lbs.), in excellent condition, the usual repositories containing normal amount of fat. A single accessory thyroid is found on the aorta just above the pericardial reflection. The heart is enlarged. The blood is of normal color.

The remaining lobe of the thyroid contains a large amount of clear syrupy colloid. Its vascularity is increased. The gland is firm, hard, yellowish gray, and translucent. The vesicles are distinct, variable in size, and all distended with colloid. The lobe weighs 27.1 grams, showing that after removal of the blood, the lobes practically had the same weight.

At the time of death, the dog, clinically, appeared normal in every way save that the thyroid lobe was enlarged and the heart-beat was forcible.

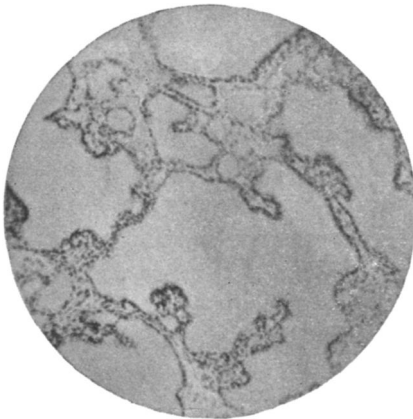


FIG. 1.

To summarize: We have a small puppy weighing roughly 2.728 kilos ( $5\frac{1}{2}$  lbs.) on October 28, 1906. Roughly, 90 mg. of a saturated alcoholic solution of iron and 14 five gr. thyroid tablets were given from October 28 to November 22, after which date he received no thyroid and no iodine other than what might have been obtained from the food.

This puppy on admission was anemic, apathetic, pot-bellied. His hair was dry and coarse, eyes weeping; he had a large symmetrical swelling of the thyroid and expansile pulsation, accompanied by a bruit. These symptoms practically cleared up in 25 days, and in the space of  $2\frac{1}{2}$  months the dog gained 3.7 kilos ( $7\frac{1}{2}$  lbs.), and became physically and mentally a normal dog save that the thyroid was still enlarged and the heart impulse forcible. The microscopic appearance of the three thyroid specimens is as follows:

(1) Specimen 1 (D-185a), removed November 7, 1906 (Fig. 1).

There is a slight general increase in the fibrous framework with band-like accentuations supporting the larger vessels. The colloid is palely staining with here and there slight vacuolation. The acini are irregularly enlarged and distorted by intra-acinar projections and invaginations of the lining epithelium. The epithelium is in general columnar; occasionally high cubical areas are noted, and over the most of the crests of the intra-acinar projections it is raised to the high columnar type. The nuclei are large, pale, vesicular, and basal. There are in places crops of apparently newly formed acini. (This variable condition of the epithelium is best explained by supposing that the return to the normal type had started already, and that had the tissue been examined before medication or the appearance of signs of clinical improvement the epithelial cells would have had the usual (glandular) uniform columnar appearance.)

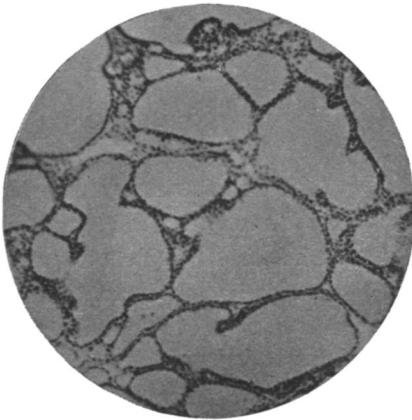


FIG. 2.

We have then a highly vascular gland with increase in the fibrous tissue, reduction in the stainable colloid, moderate papillomatous ingrowths, and invaginations of the epithelium which varies from high cubical to definitely columnar cells, and all showing large, pale, basal, round, vesicular nuclei.

(2) Specimen 2 (D—185b), removed December 11, 1906 (Fig. 2).

The stroma is quite compact, producing a notable decrease in the prominence of the fibrous tissue framework. The colloid is dense and uniform. The epithelium is generally low, cubical, except over the intra-acinar projections where it still retains a columnar type. The nuclei are generally small and deeply staining. There is no prominence of the vessels and no desquamation. The appearance now is that of a colloid adenoma, except for the occasional tufts of columnar epithelial cells capping the intra-acinar projections.

To sum up, we have four striking differences from "Specimen 1": (1) reduced prominence of the fibrous framework; (2) a nearly complete disappearance of the columnar epithelium, with return to a low cubical type; (3) a change from the large, pale, vesicular nuclei to small, deeply staining ones, and (4) an increase in the stainable colloid.

(3) Specimen 3 (D—185c), removed January 14, 1907 (Fig. 3).

The acini are large and filled with dense, uniformly staining colloid which rounds out the walls and compresses them to thin partitions, while the intra-acinar projections are compressed to cordlike masses covered with single layers of low cubical epithelium. The epithelial cells are everywhere low (flat), cubical, with small, deeply staining nuclei. Colloidlike material is visible in the lymphatics. The fibrous framework is compact and seemingly greatly decreased.

The picture now is like that seen in the pure colloid adenoma, save that the intra-acinar twigs are more numerous, and it is exactly like the picture observed in the instances where there was reason, purely from anatomical grounds, to suspect that there had previously been glandular hyperplasia.

There is now practically normal types of gland cell, nucleus and colloid, with large globular acini, into which project sprigs reduced almost to lines by their epithelial covering returning to the flat cubical type. The picture might be described as a simple adenoma or colloid goitre.

This case typifies what I had reason to suspect, purely on anatomical grounds, namely that this glandular hyperplasia may and does revert under certain conditions to a normal type of gland. In the routine examination of 250 dogs' thyroids I had seen conditions that at the time were considered "varying degrees of glandular hyperplasia" in conformity with the term suggested by Halsted and others, the vast majority of which seemed in the progressive stage, but a few, while still hyperplastic, seemed to be regressive, i. e., the hyperplasia was not universal. Indeed in a single acinus the epithelium of the main wall would be nearly normal, while that of a papillary invagination would show a columnar modification, and in other adjoining acini, all the cells would be columnar. Then, there were a few glands, enlarged, containing dense colloid, but whose acini showed many sprigs of tissue covered with flattened epithelium that seemed to be the remnants of former intra-acinar invaginations.

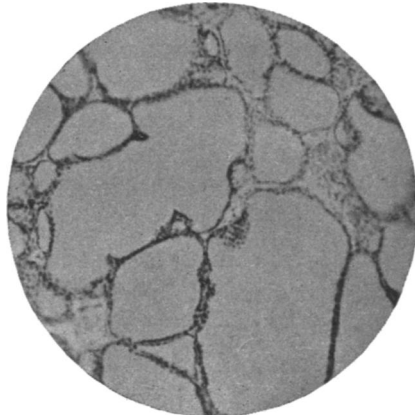


FIG. 3.

It was from these observations that I suspected a deficiency in those cases (90 per cent) which showed the progressive glandular change, and that the deficiency had been met in those few (4.5 per cent) cases which showed the regressive change. With this clew I began to inquire what this deficiency might be due to. Naturally iodine first suggested itself. But despite the enormous literature bearing on the relation of iodine to thyroid affections, both before and since Bauman's discovery, I can find no references in the available literature to instances in which these anatomic changes had been followed carefully with the microscope parallel with the administration of iodine or thyroid products.

The relation of the administration of iodine to these anatomic changes is as yet in part a weighing of evidence and a casting of opinion. In the first place one is confronted with the following questions: (1) Did the dog recover in spite of iodine medication? (2) Was his recovery hastened by the administration of iodine? Relative to the first question, it is the generally accepted opinion that iodine compounds benefit the majority of simple goitres, whether in man or in animals. (We are dealing here with simple goitre only.) Kocher states that 90 per cent of all goitres may be so improved by the administration of iodine-containing compounds as to render operation unnecessary. To show that spontaneous recovery frequently occurs we have only to recall those forms associated with puberty and pregnancy. In most of these cases it subsides. Then too we should recall in this connection the cases that have been observed in dogs where there was a return to a normal type of gland without clinical disappearance of the goitre.

It might be well here to add that when these "glandular hyperplasias" revert to a more normal type following the administration of iodine compounds, their acini, which are always enlarged, do not reduce in size, but appear even larger. This is readily seen to be so, for when a vascular, cellular acinus is stripped of its columnar epithelium and increased blood supply, its intra-acinar space becomes larger. Now while the experimental evidence shows that there is a slight gradual reduction in the size of the acini, and hence in the size of the gland as a whole, it is not probable that they could revert to a normal size; i. e., reduce in volume 20-30 times. In

other words there is every reason to believe that while iodine compounds reduce the hyperplasia—relieve the deficiency—there is but moderate reduction in the size of the gland. This reduction, in dogs, varies from  $\frac{1}{4}$ – $\frac{1}{2}$  the original volume, depending on the duration of the hyperplasia and in consequence the amount of fibrosis, and also on the age of the animal, the young, as is well known, reacting much more rapidly.

Thus the removal of the etiological factor in the production of the goitre would in nowise entail a relief from the swelling if it be well advanced, even though there are no complications. Indeed, in the dog at least, it would rather compel us to suppose a hyposecretion with a gradual absorption of the stored colloid.

The second question, as to whether iodine aided the anatomic changes, has in its favor a vast accumulation of circumstantial clinical evidence. (A critical review of this evidence will be published later.) Experiments with controls are now in progress that would seem to confirm experimentally this clinical experience and establish an anatomic basis for it, at least in the dog. The relation of the degree of "glandular hyperplasia" to the iodine content has of course interested me for some time, as it was early suspected that the iodine content might be reduced in those cases showing the hyperplasia. Through the courtesy of Dr. W. W. Williams I am able to report that the thyroid per gram weight removed at autopsy from the animal here described showed an enormous increase in the iodine content over the normal. I believe that iodine was stored in the gland, as has already been shown by many investigators to be the case in the human thyroids, following the administration of iodine. Unfortunately the iodine content of the first lobe could not be determined. From what we now know of thyreo-globulin and of Oswald's work on the iodine content of human goitres, there is reason to believe that the body economizes iodine not unlike it does iron, and indeed, carrying the analogy farther, there is reason to suspect that iodine is related to endemic goitre not unlike iron is to chlorosis. Both conditions are probably highly complex. But these two elements may be the nuclei around which the metabolic complexities of goitre and chlorosis are grouped.

In reviewing the literature one is struck with the multiplicity of



factors adduced from time to time as causal agents in the production of endemic goitre, most of which are probably without foundation. In general the views may be divided into (1) infectious; (2) metabolic. From a careful study of the writings of those most prominently engaged in the study of goitre a few deductions may be included here:

(1) That new goitrous districts are not arising apart from newly settled districts, and then only in the altitudes: in other words goitre districts remain singularly distinct.

(2) That goitrous districts are becoming less goitrous, and many previously goitrous districts are now free from goitre.

(3) That in general endemic goitre is proportionately much more prevalent among the poorer classes.

(4) That the so-called epidemics of goitre do not occur outside of goitre districts, and then among newly arrived subjects, whether man or animals.

(5) If water be associated with the cause of endemic goitre it seems rather to be due to the absence than to the presence of any particular substance in the water.

(6) Boiling the drinking water is said not to prevent the occurrence of goitre in goitrous districts.

(7) There is no record of goitre being endemic along the sea-coast.

(8) Cretinism associated with atrophy of or absence of the thyroid is about as frequent in non-goitrous as in goitrous districts, while in goitrous regions probably over 60 per cent of the cretins have enlarged thyroids.

(9) While all cretins seem to improve upon the administration of iodine, those with atrophy or absence of the thyroid do better with thyroid feeding, while those with goitre improve about as much with iodine alone, suggesting that in the one case we must supply the formed product, while in the other case the gland is able to metabolize its own product from the elementary substance.

(10) According to the case reports myxedema rarely precedes, occasionally accompanies, and frequently follows the symptom-complex of Graves' disease.

(11) It seems that the normal thyroid, like other normal organs, is more than sufficient to meet the normal physiologic needs.

(12) I have been able to find but two cases of myxedema (non-

operative) associated with tetany, suggesting that the parathyroids are relatively independent structures, thus bearing out the experimental evidence.

(13) There is no evidence for considering goitre other than a manifestation of or a reaction to a more general disorder.

(14) Carefully prepared histological data as to the occurrence and incidence of "glandular hyperplasia" in animals, both in goitrous and non-goitrous districts, are not available, but would be of the greatest value.

In concluding this report the following points may be emphasized: The histologic changes described are too striking and too rapid to be considered accidental; That lack of iodine was the essential deficiency and iodine when supplied quickly overcame the needs; that there is reason for believing that the body economizes iodine not unlike it does iron, and that it is essential to normal metabolic activities; that the determination of the relation of the "glandular hyperplasias" to the iodine content is extremely important.

This relation can be predicted from the following data: Oswald has shown that, for man and calves, the iodine content in general varies directly with the amount of colloid, and I have observed that the glandular hyperplasia in dogs varies inversely to the amount of stainable colloid; therefore the iodine content should vary inversely to the degree of glandular hyperplasia. It seems that these glandular hyperplasias are common in dogs, cattle and sheep throughout the Great Lakes District.

I wish to thank Doctors C. H. Lenhard and M. B. Bonta for their services in the operative work, and also Doctors G. W. Crile and Torald Sollmann for many favors.